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METHOD FOR TREATING ANIMALS

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(71) Applicant(s)

COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION

(72) Inventor(s)

CHRISTOPHER MAY; PHILIP LAURENCE STEWART; JOHN ALEXANDER EDGAR

(74) Attorney or Agent

PHILLIPS ORMONDE & FITZPATRICK , 367 Collins Street, MELBOURNE VIC 3000

(57) Claim

1. A method for treating an animal to at least partially remove undesirable substances from the animal or products derived from the animal the process including administering to the animal an effective amount of a cyclodextrin or modified cyclodextrin.

19. A composition for treating animals to at least partly remove undesirable substances the composition including a cyclodextrin or modified cyclodextrin, water and a low solubility magnesium salt in an amount sufficient to provide a gel.

ABSTRACT

The invention provides a method for treating an animal to at least partially remove undesirable substances from the animal or products derived from the  
5 animal the process including administering to the animal an effective amount of a cyclodextrin or modified cyclodextrin.

The invention also provides a composition for treating animals to at least partly remove undesirable substances the composition including a cyclodextrin or modified cyclodextrin, water and a low solubility magnesium salt in an amount  
10 sufficient to provide a gel.

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COMPLETE SPECIFICATION  
(TRUE COPY)

I certify that the following 18 pages are a true and correct copy of the description and claims of the original complete specification in respect of an invention entitled:

"METHOD FOR TREATING ANIMALS"

Name of Applicant(s):

COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION

PHILLIPS ORMONDE & FITZPATRICK

Attorneys for Applicant(s)

by:

*David B Fitzpatrick*

Our Ref: IRN 402615

METHOD FOR TREATING ANIMALS

The present invention relates to a method for the treatment of animals and is particularly concerned with the treatment of animals to remove undesirable substances such as chemical toxins. The invention also relates to a composition for use in treatment of animals.

Unwanted dietary components such as toxins can affect the health of animals and may taint or adversely affect the quality of animal products such as meat and milk. Toxins which may be consumed by animals during grazing are a particular problem.

For example, grazing of ryegrass infected by certain bacteria gives rise to serious and often fatal neurological diseases in livestock. Annual ryegrass toxicity (ARGT) is understood to be caused by the Corynetoxins produced by Clavibacter sp., whereas perennial ryegrass toxicity is believed to be produced by another class of toxins known as the Lolitrem, such as Lolitrem B. Previous attempts have been made to treat annual ryegrass toxicity using chlordiazepoxide (Norris R.T. Australian Veterinary Journal Vol 57, June 1981, p302) however such treatment requires significant post treatment support and is generally impractical and uneconomic for use in livestock. Toxins from Aspergillus Flavis sp. including Aflatoxins also cause acute toxicity.

Furthermore, more recent developments in regard to food safety have resulted in a need to reduce the amount of undesirable natural residues in animal products.

We have found that a cyclodextrin or modified cyclodextrin may be used to treat an animal in order to scavenge unwanted substances from the animal, animal tissue or animal product.

In particular, we have found experimentally that the cyclodextrins strongly bind to toxins which cause poisoning of livestock, to reduce the effects of these toxins. Treatment of the animal with a cyclodextrin or modified cyclodextrin may also result in the removal of contaminants such as carotene or carotene derivatives from the fat of the animal and thereby reduce yellowing of the fat.

Accordingly, in one aspect, the present invention provides a method for treating an animal to at least partially remove undesirable substances from the

animal or products derived from the animal comprising administering to the animal an effective amount of a cyclodextrin or a modified cyclodextrin.

More particularly, the present invention provides a method for the treatment or prophylaxis of the poisoning of livestock animals by administration 5 thereto of an effective amount of a cyclodextrin or a modified cyclodextrin.

The cyclodextrin may be selected from  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin,  $\gamma$ -cyclodextrin or derivatives thereof.

Examples of cyclodextrin derivatives may be selected from alkylated cyclodextrins including alkylated- $\beta$ -cyclodextrins such as 2,6-di-*o*-methyl- $\beta$ -cyclodextrins and trimethyl- $\beta$ -cyclodextrin; hydroxyalkylated cyclodextrins such as 10 2-hydroxypropyl- $\beta$ -cyclodextrin and hydroxyethyl- $\beta$ -cyclodextrin; and cyclodextrin polymers which are products containing two or more cyclodextrin units such as a copolymer formed between  $\beta$ -cyclodextrin and epichlorohydrin.

The cyclodextrin may be administered in the form of an aqueous solution 15 however we have found that multiple administration is required to maintain a safe and effective level of the cyclodextrin. For example in treating ARGT we found that improved animal survival was observed only when the cyclodextrin level is maintained in the circulation by two intraperitoneal administrations over 24 hours. The need for multiple administrations significantly increases the cost of treatment 20 and where many animals are affected multiple treatment is often impractical.

We have now found that the use of a cyclodextrin composition in the form of an aqueous gel containing a magnesium salt allows effective treatment with a single administration.

In a particularly preferred embodiment of the invention we provide a 25 composition for treating animals to at least partially remove undesirable substances the composition comprising a cyclodextrin (which may be selected from those referred to above) and a magnesium salt and water wherein the composition is in the form of a gel.

The preferred magnesium salts are of low water solubility so that together 30 with the cyclodextrin and appropriate amount of water a gel is formed. Most preferably the magnesium salt component will include an organic acid salt and it is particularly preferred that the acid portion of the salt is an acid derived from a carbohydrate such as sugar. Magnesium gluconate is the most preferred.

3a

The presence of the magnesium salt is particularly advantageous as we have found that it significantly reduces convulsions suffered by the animal and

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stabilises the animal for sufficient time to enable cyclodextrin to produce a reduction in the levels of free and membrane-bound toxin in the animal.

The amount of magnesium ion present is generally sufficient to provide anticonvulsant activity. Typically the amount of magnesium ion for providing the 5 desired anticonvulsant activity will be greater than the amount of organic acid/magnesium to provide the desired gel consistency. In such cases it is preferred to use a portion of the magnesium in the form of an inorganic salt particularly magnesium sulphate.

The amount of magnesium present in each form will depend on the 10 concentration of cyclodextrin (and hence the dose required), and the consistency of the composition. The desired dose of magnesium ion is typically in the range of from 1 to 400 mg/kg and preferably 5 to 100 mg/kg most preferably 40 mg/kg and a weight ratio of cyclodextrin to magnesium ion of 200:1 to 1:1.

In a preferred embodiment of the composition of the invention the 15 composition contains 100 parts by weight cyclodextrin, 1 to 500 parts by weight magnesium ion and wherein the magnesium ion is present as an organic acid salt and an inorganic salt, particularly magnesium sulphate, wherein the ratio magnesium in these forms is in the range of from 1:10 to 10:1.

The animal treated according to the invention is preferably a livestock 20 animal although the invention may also be useful in treating domestic animals such as cats and dogs suffering from the effect of toxins. The animal is most preferably a ruminant animal selected from sheep, cattle or goats, although other livestock such as horses may also be treated in accordance with the invention.

The treatment may be therapeutic or prophylactic. We have found that the 25 treatment method of the present invention may be used to rescue animals which have been poisoned by toxin.

Parenteral delivery may be used. The cyclodextrin or modified cyclodextrin may be administered subcutaneously, intraperitoneally, intraruminally, intramuscularly, intravenously. Intrapertoneal administration is particularly 30 preferred. The cyclodextrin may be dispensed by a slow release device, for example, that described in Australian Patent No. 520409 however the use of the magnesium salt gel composition generally obviates the need for such slow

release devices. The invention may also be used in treatment of other poisoning diseases caused by toxins capable of forming an inclusion complex with cyclodextrin or a modified cyclodextrin.

- As previously indicated, the treatment of the present invention may be
5. used to scavenge agents to decrease burden of residues from the animal. For example, the method may be used to strip carotene or carotene like molecules from the fat of the animal so as to improve the appearance of meat obtained from the animal or to treat Vitamin A toxicity.

- A number of other poisoning diseases may be amenable to treatment with
- 10 cyclodextrin derivatives. These include, in particular poisoning caused by substances able to penetrate the cavity of the cyclodextrin molecule and form inclusion complexes. The suitability of a particular cyclodextrin or modified cyclodextrin for particular toxins can be determined by testing *in vitro*. Further examples of toxins for which treatment is suitable include the fumonisin mycotoxins, aflatoxins, simplexin and related substances and the lolitremes and other tremorgens and toxins produced by *Acremonium* and *Penicillium* spp.
- 15

The amount of cyclodextrin or modified cyclodextrin which is administered to the animal is in the range of 10 g/kg to 1 µg/kg, preferably 10 to 400 mg/kg.

- In order that the invention may be readily understood the following non-limiting examples are provided.

Examples

The preparation of hydroxypropyl β cyclodextrin

Hydroxypropyl β cyclodextrin was prepared by a procedure derived from that of Pitha J. et al (1986) described below.

- 25      β cyclodextrin (1 kilogram) was suspended in water (2.5 litres) and cooled with an ice bath. A chilled solution of sodium hydroxide (280 g in 800 ml water) was added to the suspension of β cyclodextrin. Epoxy propane (700 ml) was added in four aliquots over a period of four hours during which time the reaction was cooled with ice. The reaction was continually mixed for 15 hours during
- 30      which time it was slowly allowed to come to ambient temperature. The reaction was then neutralised by passing the reaction mixture through an ion exchange column containing Amberlite IRN 77(H<sup>+</sup>). The solution was then diluted with

water to a volume 20 litres and dialysed using an Amicon Spiral cartridge S1Y3 (nominal MW cut off 3000). The resulting dialysate was evaporated to dryness and dissolved in ethanol (2 litres), this ethanolic solution was filtered and then added dropwise into dry acetone (20 litres). The precipitated white solid was 5 collected, washed with dry acetone (500 ml) and dried under vacuum to a white powder (1.1 kg) Hydroxypropyl  $\beta$  cyclodextrin, average degree of substitution = 1 (ie 7 hydroxypropyl groups per cyclodextrin)

H-MR(D20) $\delta$  1.1d(21),3.4-4.1(63),5.05(4.5)5.2(2.5)

Example 1

10 This example demonstrates preparation of a cyclodextrin composition in accordance with the invention.

The formulation is prepared using a 1 litre food blender according to the following procedure.

15 Hydroxypropyl  $\beta$  cyclodextrin (250 ml, 50%) was placed in a blender and mixed with magnesium gluconate (100 g). To this magnesium sulphate (200 ml, 50%) was added and the suspension thoroughly mixed. Another aliquot of magnesium gluconate (100 g) was slowly added, followed by water (80 ml) and the mixture was again thoroughly mixed.

20 The above mixture (total volume ~ 650 ml) was then sterilised and packaged for use at a dose rate of 0.5 ml per kg of live weight.

Examples 2-7 - Sheep Pen Trials

Materials and Methods

The disease model

25 The disease annual ryegrass toxicity (ARGT) has many different scenarios in the field, all of which result in a similar outcome varying only in the degree of severity, which is reflected in the percentage of animals killed. The time from start of exposure to the observation of clinical signs can vary from as short as several days to months, depending on the level and frequency of toxin intake.

30 In establishing a model of the disease a relatively short period to clinical signs was chosen for practical and animal welfare reasons. The toxic principles of ARGT are the corynetoxins a family of uridine glycolipids which specifically inhibit the initial step in glycoprotein assembly. This process occurs long before

any biological markers are affected or clinical signs appear. The tunicamycins are another family of uridine glycolipids which are structurally very similar to the corynetoxins; Indeed the two families overlap to a degree, with some components being identical. The tunicamycins are also capable of causing an ARGT-like condition in sheep and other animals at the same dose level as the corynetoxins. Both strongly inhibit the same transferase enzyme and therefore can be considered pharmacologically and toxicologically identical in their effect. The commercial availability of the tunicamycins in a pure form makes their use desirable in any preliminary work on ARGT, and hence their use in this work.

10 Tunicamycin was used throughout the sheep pen trials to induce the disease ARGT. The tunicamycin was administered parenterally for reasons of reproducibility.

15 The disease model chosen was shown to be accurate, in producing a predetermined level of effect, and highly reproducible given the natural variability in tolerance to ARGT toxins that occurs in sheep. The general aetiology was as follows.

Sheet were administered with tunicamycin according to their body weight, animals were given two or three doses 24 hours apart. After four days from the initial injection clinical signs characteristic of the disease were generally observed, on the fifth day the disease "peaked" in its intensity, and the untreated animals continued to display signs for up to four days later. All animals appeared "normal" after day ten, and were kept under regulation observation to at least day 14.

#### Experimental Treatments

#### Cyclodextrin Treatments

25 Hydroxypropyl- $\beta$ -cyclodextrin, 2,6-O-dimethyl  $\beta$  cyclodextrin and  $\beta$ -cyclodextrin epichlorohydrin copolymer were administered as 50% solutions and were given intraperitoneal except where specified differently.

#### Formulations of cyclodextrins with magnesium salts

30 A prolonged release injectable gel like formulation was made by mixing a 50% solution of Hydroxypropyl  $\beta$  cyclodextrin with magnesium gluconate and magnesium sulphate (as described above). This formulation was given via intraperitoneal injection.

Sheep Pen TrialsExample 2

Hydroxy propyl  $\beta$  cyclodextrin was given once per day with sheep challenged with tunicamycin (LD25).

- 5       Forty-five wether sheep were randomly distributed into three groups of fifteen according to live weight. All groups were administered with three doses of 6  $\mu\text{g}/\text{kg}$  tunicamycin S.C. one dose per day for three days. On day two of the trial one of the groups was administered with 100 mg/kg Hydroxypropyl  $\beta$  Cyclodextrin I.P. this was repeated at approximately 24 hour intervals for four days. The  
10      animals were monitored as to their condition daily or more often.

Example 3

2,6-O-dimethyl  $\beta$  cyclodextrin administered I.P. once per day in sheep challenged by tunicamycin LD30.

- 15      This cyclodextrin derivative was administered at 100 mg/kg I.P. once per day at 24 hour intervals at the same schedule as for hydroxypropyl  $\beta$  cyclodextrin.

Example 4

Hydroxypropyl  $\beta$  cyclodextrin given three time per day by intravenous injection in sheep challenged with tunicamycin LD30.

- 20      In addition to the three groups in trial 1 and 1a another group of 10 sheep were administered with three doses of tunicamycin (6  $\mu\text{g}/\text{kg}$  S.C.) one dose per day for three days. The group was administered with hydroxypropyl  $\beta$  cyclodextrin (15 mg/kg I.V.) three times per day for four days after day one.

Example 5

- 25      Hydroxy propyl  $\beta$  cyclodextrin given twice per day I.P. with sheep challenged with tunicamycin (LD60).

Thirty sheep were randomly distributed into three groups of ten according to live weight. Each group was administered with two doses of 11  $\mu\text{g}/\text{kg}$  tunicamycin S.C. 24 hours apart on days one and two. Starting on day three one group of sheep were administered with 100 mg/kg hydroxypropyl  $\beta$  cyclodextrin  
30      I.P. twice per day for three days. The condition of all animals was monitored daily for 14 days.

Example 6

Hydroxypropyl  $\beta$  cyclodextrin given I.P. and magnesium sulphate given I.M. both given twice per day in sheep challenged with tunicamycin LD60.

- In addition to the above one group of ten sheep were on days three to five administered with hydroxypropyl  $\beta$  cyclodextrin 100 mg/kg I.P. and 50% magnesium sulphate 200 mg/kg I.M. both twice per day.
- 5

Examples 6 and 7

Thirty sheep were randomly distributed into three groups of 10 sheep, each of these groups was administered with two doses of 12  $\mu\text{g}/\text{kg}$  tunicamycin S.C. 24 hours apart on days one and two. One group served as untreated control animals

10

two groups were treated individually as described in the trials three and 4.

Example 6

$\beta$  cyclodextrin epichlorohydrin copolymer given twice a day to sheep challenged with tunicamycin (LD 60).

- One of the above groups was administered with  $\beta$  cyclodextrin epichlorohydrin copolymer 100 mg/kg interperitoneal twice per day for three days, on days three, four and five. The condition of the sheep was monitored daily or more often for 14 days.
- 15

Example 7

- Hydroxypropyl  $\beta$  cyclodextrin in Mg gluconate gel administered once per day to sheep challenged with tunicamycin (LD60).
- 20

One of the above groups was administered with hydroxy propyl  $\beta$  cyclodextrin/magnesium gluconate gel 0.5 ml per kg live weight (initial weight) on days four and five of the trial (two sheep given third dose on days six). The condition of the sheep was monitored daily or more often for 14 days.

ResultsAnimal Survival

<u>Example</u>	<u>Animals</u>	<u>Surviving</u>	<u>Died</u>	<u>Euthanased</u>
<u>Example 2</u>	Control	11	3	1
	Treated	14	1	0
<u>Example 2a</u>	Treated	12	3	0
<u>Example 3</u>	Treated	8(10)	1	1
<u>Example 4</u>	Control Treated	4(10) 9	5 1	1 0
<u>Example 5</u>	Treated	10	0	0
<u>Example 6</u>	Control Treated	4 9	2 1	4 0
<u>Example 7</u>	Treated	9	1	0

Field Trials on Efficacy of the AntidoteThe Use of Hydroxypropyl- $\beta$ -cyclodextrin in the Form of a Magnesium Gluconate Gel Vs as a Solution

Hydroxypropyl  $\beta$  cyclodextrin is a very water soluble molecule and when  
5 administered parenterally is rapidly excreted in the urine. In rats and dogs given hydroxypropyl  $\beta$  cyclodextrin intravenously plasma half lives were measured at 0.4 and 0.8 hours respectively and 90% was excreted in the urine within 4 hours.

Another  $\beta$  cyclodextrin derivative, 2,6 di-O-methyl  $\beta$  cyclodextrin, is also largely excreted in the urine within six hours when administered intravenously and  
10 when administered intramuscularly it was completely excreted within 24 hours.

In our work in sheep hydroxypropyl  $\beta$  cyclodextrin when administered as a 50% solution intraperitoneal, could be detected in the plasma for up to 15 hours after administration.

From the sheep pen trials it was determined that a beneficial effect-in  
15 terms of significantly increasing animal survival is obtained when hydroxypropyl  $\beta$  cyclodextrin is continuously maintained within the circulation. This necessitates a solution being given twice by intraperitoneal injection during a given 24 hour period.

In sheep pen treatment trials with sheep affected by annual rye grass  
20 toxicity (ARGT) intravenous administration of hydroxypropyl  $\beta$  cyclodextrin had to be carried out many times per day to increase the survival rate of animals. Also other  $\beta$  cyclodextrin derivatives such as 2,6-O-dimethyl also require multiple daily injections to be effective in sheep with ARGT. The administration of multiple daily injections to animals with ARGT in the field is both impracticable and undesirable,  
25 due to stress precipitating the physical condition of the disease.

The formulation of hydroxypropyl  $\beta$  cyclodextrin into a magnesium gluconate gel as described in Example 1 enables the maintenance of hydroxypropyl  $\beta$  cyclodextrin in the circulation of sheep for 24 hours from a single intraperitoneal injection. This formulation was shown to be as effective as twice  
30 daily injections of solution of hydroxypropyl  $\beta$  cyclodextrin in increasing the survival of sheep affected mortally with ARGT.

The magnesium salts provide anticonvulsant activity in sheep affected by ARGT when administered intramuscularly and to a lesser extent when given intraperitoneal. Although this property of magnesium sulphate can block convulsions for an average of 12 hours in most cases, animals relapse into a

- 5 state of ARGT once the magnesium salt has been excreted. Thus magnesium salt administration alone prolongs in the short term the life of animals affected by ARGT, but is only moderately successful in rescuing sheep when continued to be administered. Repeat administrations also have an ever decreasing period of effect.

- 10 The role of the magnesium salts in the hydroxypropyl  $\beta$  cyclodextrin formulation is to suspend the hydroxypropyl  $\beta$  cyclodextrin in an injectable gel matrix which in itself is biocompatible with the method of administration. This is believed to prolong the absorption of the cyclodextrin into the circulation and also to act as an anticonvulsant to temporarily block convulsions in animals displaying 15 the signs of ARGT and thus bring these animals into a stable state and allow the cyclodextrin to redistribute the ARGT toxins and aid the recovery of the animal.

- In this role the magnesium salt used is magnesium gluconate which forms a gel when used at the concentration described in the formulation. Magnesium gluconate is used together with magnesium sulphate in order to bring the total 20 magnesium concentration to the level to provide an anticonvulsant effect.

The combination of hydroxypropyl  $\beta$  cyclodextrin and magnesium salt has been shown to be synergistic in its ability to rescue animals affected by ARGT.

Examples 8 and 9

Sheep Field Trials

25 Introduction

- The use of a treatment for ARGT is based on the field observation that when a farmer first notices that his sheep are affected by ARGT there is a period of about 4-5 days to what is termed peak deaths, during this period and the following five days most deaths occur. The scenario under which the antidote is 30 designed to be used, is when a farmer first observed ARGT in his sheep. At this point they can be moved, and treated, thus saving the majority that would simply be lost by just moving them.

Experimental Design

The basic protocol used in field testing of the ARGT antidote was as follows: an ARGT outbreak, the affected animals were yarded and a controlled experimental procedure carried out. The details of the outbreak and the

- 5 procedures used are outlined for each trial. Antidote was administered as the gel formulation of Example 1 at a rate of 0.5 ml/kg live weight given by I.P. injection. Details of the condition of the animals were recorded during the week after treatment and if necessary follow up calls were made to record any further developments.

10 Example 8

70 ewes were held in a separate paddock from the main mob. The 70 sheep were later found to have been grazing on toxin-containing annual ryegrass and one sheep was observed to be in a convulsive state. The sheep were moved to yards. The convulsive sheep died when moved. One further recumbent sheep

- 15 treated shortly after showing signs and the other 69 sheep were put through a race and alternate sheep treated and marked. One sheep was in a convulsive state and was also treated. Thus the trial consisted of a total of 35 untreated control animals and 35 treated animals including two in a state of convolution.

- 20 The sheep were kept in yards overnight and the treated group readministered with the antidote the next day. The sheep were kept in yards and given hay and water for four more days during which time six of the untreated group died and three others displayed clinical signs, only one of the treated animals displayed clinical signs during this period. After one week the sheep were released to a safe paddock, none of the surviving sheep at this stage appeared affected.

25 A total of six untreated animals died during the course of the outbreak, one of the treated animals died. This situation remained unchanged over the following month.

Example 9

- 30 A mob of seriously ARGT effected sheep was driven to yards for treatment trial, 12 sheep displayed clinical signs on the way, and were carried to the yards. Sheep were split into two groups: Group 1 the 12 animals which displayed clinical

signs during being moved, and Group 2 the remaining 140 animals. In Group 1, six animals were treated and six remained as untreated controls. In Group 2, 73 animals were treated and 67 designated control animals. The following day five of the Group 1 treated and 71 of the Group 2 treated animals were retreated, 5 three animals having died. The sheep were kept in yards for two more days during which time a total of four control animals from Group 1 and 18 from Group 2 died compared to one treated animal from Group 1 and eight from Group 2. The sheep were then released to a safe paddock, where all sheep appeared to be able to move without difficulty. No further losses were reported when farmer 10 was contacted a week later.

Thus, 79 animals were treated and 73 were used as untreated controls. 70 of the treated and only 51 control animals survived.

Examples 10 and 11

Cattle Field Trials

15 Example 10

This case of ARGT was identified after a prolonged series of losses from feeding cattle ryegrass hay. 30 cattle had died over several weeks prior to ARGT being confirmed, due to toxic hay being continuously fed after animals started to exhibit clinical signs and die. When ARGT was confirmed there were seven 20 animals displaying the characteristic nervous clinical signs. The following day five of the seven animals were laterally recumbent and these were treated. The antidote was administered once at 0.5 ml per estimated kg live weight I.P. The two remaining animals displaying only mild clinical signs were left as untreated controls. All five treated animals recovered to be "normal" within 48 hours and 25 survived, of the two untreated controls the condition of one deteriorated and died, the other control survived.

Example 11

Four dairy cattle which were all showing signs of ARGT. Three were recumbent and one standing displaying tremors. Two of the recumbent animals 30 were treated once with 200 mls of antidote (~400 kg live weight) and kept in yards. Both treated animals recovered to be normal within 48 hours, the one untreated animal that was recumbent died.

The claims defining the invention are as follows:

1. A method for the treatment or prophylaxis of the poisoning of livestock animals by administration thereto of an effective amount of a cyclodextrin or a modified cyclodextrin.  
5
2. A method according to claim 1 wherein the cyclodextrin or modified cyclodextrin is administered at a dose of from 1 µg to 10 g per kg of animal body weight.
3. A method according to claim 2 wherein the cyclodextrin or modified cyclodextrin is administered in an amount of from 10 mg to 400 mg per kg of animal body weight.  
10
4. A method according to any one of claims 1 to 3 wherein the cyclodextrin or modified cyclodextrin is selected from the group consisting of  $\beta$  cyclodextrin hydroxyalkylated- $\beta$ -cyclodextrins and cyclodextrin polymers.
- 15 5. A method according to claim 4 wherein the cyclodextrin or modified cyclodextrin derivative is selected from the group consisting of hydroxypropyl- $\beta$ -cyclodextrin; 2,6-di-O-methyl- $\beta$ -cyclodextrin and copolymers formed between  $\beta$ -cyclodextrin and epichlorohydrin.
- 20 6. A method according to claim 1 wherein the animal is a ruminant animal.
7. A method according to claim 1 wherein the animal is a sheep.
8. A method according to claim 1 wherein the cyclodextrin or modified cyclodextrin is present in a composition including water and a low solubility magnesium salt, the low solubility magnesium salt provide a gel.
- 25 9. A method according to claim 8 wherein the low solubility magnesium salt is a magnesium salt of an acid derived from a carbohydrate.
10. A method according to claim 8 wherein the magnesium salt is magnesium gluconate.
- 30 11. A method according to claim 9 wherein the composition further contains magnesium sulphate the total magnesium ion content being sufficient to provide an anticonvulsant effect.
12. A method according to claim 11 wherein magnesium ion is administered at a rate of from 5 to 100 mg/kg based on magnesium.

13. A method according to any one of the previous claims wherein the cyclodextrin or modified cyclodextrin is administered subcutaneously, intraperitoneally, intraruminally, intramuscularly or intravenously.
14. A method according to claim 13 wherein the cyclodextrin or modified cyclodextrin is administered by peritoneal injection.
15. A method according to claim 1 wherein the animal is suffering from the effects of toxins ingested by the animal during grazing.
16. A method according to claim 14 wherein the toxin is capable of forming an inclusion complex with the cyclodextrin or modified cyclodextrin.
17. A method according to claim 1 wherein the animal is suffering from poisoning caused by a toxin selected from the group consisting of corynetoxins tunicamycins, lolitrem, fumonisins, mycotoxins, aflatoxins and other tremogens and toxins produced by Acremonium and Penicillium spp.
18. A method according to claim 1 wherein the animal is suffering from annual rye grass toxicity or perennial rye grass toxicity.
19. A composition for treating animals to at least partly remove undesirable substances the composition including a cyclodextrin or modified cyclodextrin, water and a low solubility magnesium salt in an amount sufficient to provide a gel, and further wherein the magnesium salt is a magnesium salt of an organic acid of a carbohydrate.
20. A composition according to claim 19 wherein the magnesium salt is magnesium gluconate.
21. A composition according to claim 19 wherein the composition contains a further magnesium salt the total amount of magnesium ion being sufficient to provide an anticonvulsant effect when the composition is administered in an amount 400 mg cyclodextrin or modified cyclodextrin per kg of animal body weight.
22. A composition according to claim 19 wherein the further magnesium salt is magnesium sulphate.
23. A composition according to any one of claims 19 to 21, wherein the cyclodextrin or modified cyclodextrin is selected from alkylated  $\beta$ -cyclodextrins, hydroxyalkylated cyclodextrins and cyclodextrin polymers.

24. A method according to claim 1 substantially as herein described with reference to any one of the Examples.
25. A composition according to claim 19 substantially as herein described with reference to any one of the Examples.

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10 DATED: 21 May, 1999

PHILLIPS ORMONDE & FITZPATRICK  
Attorneys for:  
COMMONWEALTH SCIENTIFIC & INDUSTRIAL  
15 RESEARCH ORGANISATION

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